

Maternal Intake of Natto, a Japan's Traditional Fermented Soybean Food, during Pregnancy and the Risk of Eczema in Japanese Babies

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ABSTRACT

Background: There are reports that the maternal diet during pregnancy may affect development of babies' eczema. We sought to investigate the association between the maternal diet during pregnancy and the risk of eczema in infancy in Japan.

Methods: A birth cohort was set up at 2 hospitals in Chiba city. Dietary habits concerning fish, butter, margarine, yogurt and natto during pregnancy was obtained from mothers just after delivery. The intake frequencies of these foods were classified into four groups: 1) daily, 2) 2-3 times a week, 3) once a week and 4) once a month or less. Diagnosis of eczema at 6 months of age was made by the presence of an itchy rash that persisted more than two months.

Results: Valid data on 650 mother-baby pairs were obtained. No relationship between frequencies of the maternal intake of fish, margarine and yogurt during pregnancy and the onset rate of the babies' eczema were observed. For butter consumption, the incidence of babies' eczema was significantly higher in the group with daily intake than in those with an intake 2-3 times a week or less ($p = 0.044$). For natto, incidence of babies' eczema was significantly lower in the group with everyday intake than those eating it 2-3 times a week or less ($p = 0.020$).

Conclusions: High frequency intake of natto during pregnancy possibly reduces the incidence of eczema in children at 6 months of age.

KEY WORDS

atopic dermatitis, food, infant, natto, pregnancy

INTRODUCTION

It has been suggested that the maternal diet during pregnancy might be one of the factors that influence fetal immune responses associated with childhood allergies.¹ There are studies on diet during pregnancy and babies' eczema in Europe, reporting that the maternal intake of fish prevents the babies' eczema.²⁻⁵ On the other hand, no relationship has been recognized between the maternal intake of fish and the atopic eczema of babies at the third or the fourth

months after birth in Japan.⁶ The maternal intake of margarine was reported to front the risk of eczema in children two years of age in Germany⁴ and it was also reported to have no relationship with the atopic eczema of children at five years of age in Finland.⁷ There were reports that the maternal intake of meat led to the risk of the babies' atopic eczema in Japan, a relationship not recognized in Europe.⁶ In this way, it was considered that the relationship between the maternal diet during pregnancy and the babies' eczema was different among areas with different dietary hab-

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its and races.

There were only a few studies on the maternal diet during pregnancy and the babies' eczema in Japan. In addition, because Japan has such unique dietary habits, the research of diet including the foods unique to Japan was necessary. Therefore, in this study we included natto, which is unique to Japan, to the typical foods being so far tested, and investigated the relationships between frequencies of the maternal intake of these foods during pregnancy and the eczema in infancy.

METHODS

STUDY SUBJECTS

A prospective birth cohort study of 882 newborn infants was set up in Kawatetsu Chiba Hospital and Chiba University Hospital in Japan from January 2007 to May 2008. In the obstetrical section, pregnant women who were around 36 gestations were recruited. All participants provided written, informed consent to participate in this study. This study was approved by the ethics committee of Chiba University Graduate School of Medicine.

DATA COLLECTION

The pregnant women from whom consent was received were asked to answer the questionnaire including dietary habits during pregnancy and their family's history of allergic diseases while hospitalized for delivery. The intake frequencies of fish, butter, margarine, yogurt and natto were classified into four groups as the dietary habit during pregnancy: 1) daily, 2) two to three times a week, 3) once a week and 4) once a month or less. The allergic histories of the parents, siblings, and grandparents of the babies were investigated. The questionnaires about babies' skin condition and feeding methods at the fourth and the sixth months after birth were given to mothers with return-mail envelopes on discharge from hospital. Questionnaires were sent to our department by mail when babies were fourth and sixth months of age. The eczema of the babies was investigated by the questionnaire concerning babies at the sixth months after birth. The diagnosis of eczema was made by observation of a rash accompanied by itching, persisting more than two months.

STATISTICAL METHODS

SPSS Statistics 17.0 software (SPSS Inc., Chicago, Illinois, USA) was used for statistical analysis of this research. The Chi-square test and Mann-Whitney U test were used for the comparison of the backgrounds of the mothers and their babies. The intake frequencies of the five foods and the incidence of eczema were analyzed using a multiple logistic regression analysis.

RESULTS

BACKGROUND CHARACTERISTICS

Of the 882 pairs enrolled, 650 pairs gave valid responses to the questionnaires about babies for the period of six months after birth. One hundred and fourteen babies (17.5%) had eczema at 6 months of age (Table 1). As far as the mother's background was concerned, the number of mothers who answered that they had a history of atopic dermatitis tended to be larger in a group with babies who had eczema ($p = 0.070$). In relation to the baby's background, season of birth showed a significant association with eczema ($p < 0.001$); eczema was more frequent in babies born in autumn (September, October, November) and winter (December, January, February) than those born in spring (March, April, May) and summer (July, August). Also, a significant difference concerning gender was observed between two groups with and without eczema, and the proportion of male infants was significantly larger in the group with eczema ($p = 0.040$). No significant difference was observed in other items (Table 1).

DIETARY INTAKE AND ECZEMA

No significant relationship was recognized between the intake frequencies of butter, margarine and yogurt during pregnancy and the incidence of the babies' eczema (Table 2). A lower natto intake frequency was significantly associated with a higher eczema incidence was observed (Trend test, $p = 0.021$). This tendency was significant in a multiple logistic regression analysis as well, with the mother's atopic dermatitis history, season of birth, and the baby's gender as variables ($p = 0.020$). A trend that the lower the fish intake frequency was, the higher the onset rate of eczema was recognized (univariate analysis: $p = 0.056$, multivariate analysis: $p = 0.093$).

In order to see the relationship between high frequency intake and the incidence of eczema, we performed a comparison between everyday intake and intake of two to three times a week or less. When the frequencies were classified into "everyday" and "two or three times a week or less" there were significant correlation ($p < 0.05$) among the five foods (Table 3); fish and margarine; fish and natto; butter and yogurt, margarine and yogurt; and yogurt and natto. In multiple logistic regression analysis, in addition to the mother's atopic dermatitis, season of birth, and the baby's gender, we included five independent terms for food intake frequency and the five interaction terms shown above. The incidence of the eczema in the group taking natto everyday was 6.7% and that in the group taking it two to three times a week or less was 18.7%, and a significant difference was found in a multiple logistic regression analysis as well ($p = 0.020$) (Table 4). The incidence of eczema of the group taking butter everyday was 35.0% and that of

Table 1 Characteristics of 650 mother-child pairs grouped according to infantile eczema

	Infant with eczema (n = 114)	Infant without eczema (n = 536)	p-value
Maternal characteristics			
Age (years)	33	33	0.960
History of allergy (%)	73/113 [†] (64.6)	321/525 [†] (61.1)	0.553
History of atopic dermatitis (%)	25/113 [†] (22.1)	79/520 [†] (15.2)	0.070
BMI before delivery	20.0	20.3	0.369
Food elimination during pregnancy (%)	11/113 [†] (9.7)	50/532 [†] (9.4)	0.912
Baby characteristics			
Weight (g)	3027.5	2959.1	0.107
Gender (% male)	64/113 [†] (56.6)	243/528 [†] (46.0)	0.040
Gestation (week)	39.4	39.3	0.715
Caesarean birth (%)	35/119 [†] (31.3)	148/526 [†] (28.1)	0.508
Nutrition until 4 months: Breast feeding (%)	11/111 [†] (9.9)	77/530 [†] (14.5)	0.199
Mixed feeding (%)	100/111 [†] (90.1)	453/530 [†] (85.5)	
Seasons of birth: Spring (%)	20/114 (17.5)	175/534 [†] (32.8)	<0.001*
Summer (%)	18/114 (15.8)	132/534 [†] (24.7)	
Autumn (%)	41/114 (36.0)	110/534 [†] (20.6)	
Winter (%)	35/114 (30.7)	117/534 [†] (21.9)	

Values represent numbers of participant with percentages in parentheses or medium value. There was no baby who fully fed formula. BMI, Body mass index.

Spring: March, April, May; Summer: June, July, August; Autumn: September, October, November; Winter: December, January, February.

[†] Exact number of infants was shown when information was lacking in some infants and mothers.

*p-value of chi-square test of 2 (with or without eczema) × 4 (seasons) contingency table.

the group taking it two to three times a week or less was 17.0% ($p = 0.044$ for crude OR). The difference was not reach to the significant level in a multiple logistic regression analysis ($p = 0.053$). None of the intake of fish, margarine and yogurt was significantly related with the incidence of eczema (Table 4).

DISCUSSION

Natto, a traditional Japanese food made from soybeans fermented with *Bacillus subtilis* is unique to Japan, and this research is the first to report on the maternal intake of natto during pregnancy and its effect on the babies' eczema. The maternal intake of natto during pregnancy was associated with a low incidence of eczema at 6 months of age. Development of eczema might not be affected by a solitary food such as natto, but might depend on whole dietary habits of mothers. A research paper in Japan reported that dietary habits close to European ones led to allergic rhinitis.⁸ In this study, in a multiple logistic regression analysis to exclude confounding effects of other foods studied, an effect of natto intake during pregnancy on incidence of eczema in infancy was statistically significant. Thus, frequent natto consumption possibly shows distinct protective effect on the babies' eczema development although a possibility that natto intake is a surrogate marker for the frequency of eating Japanese food remains.

No relationship between the maternal intake of

margarine during pregnancy and an incidence of the babies' eczema was observed, just as the report from Finland.⁷ Meanwhile in Japan, it was reported that the intake of n-6 fatty acids, linoleic acid in particular, which are typically included in margarine, increases the risk of eczema in babies ages 16 to 24 months.⁹ The relationship between the maternal intake of margarine during pregnancy and the babies' eczema has not been concluded. The relationship between the maternal intake of yogurt during pregnancy and the babies' eczema was not recognized in a German⁴ nor in a Japanese study.¹⁰

In our study, no significant association was observed between fish consumption and eczema. There are several reports abroad that the intake of fish decreases the risk of the babies' eczema.²⁻⁵ Furthermore, there are many reports¹¹⁻¹⁵ that n-3 fatty acids (included largely in fish) in breast milk and serum of mothers is related to the decrease of the babies' eczema. Meanwhile, in the research by Miyake *et al.* in Japan, no relationship was recognized between the maternal intake of fish during pregnancy and the atopic eczema of the babies in the third or the fourth month after birth.⁶ Our study shows a similar result to that of Miyake *et al.*, suggesting the effect of maternal fish intake on babies' eczema is different between Japan and Western countries.

Daily maternal intake of butter during pregnancy showed a trend for increased incidence of eczema

Table 2 Maternal intake frequencies of the five foods during pregnancy and the trend of eczema incidence

	Infant with eczema <i>n</i> (%)	Infant without eczema <i>n</i> (%)	Crude OR		Adjusted OR	
			OR	<i>p</i> -value for trend	aOR	<i>p</i> -value for trend
Fish						
Everyday	8 (24.2)	25 (75.8)	1		1	
2-3 times/week	74 (18.1)	334 (81.9)	0.478	0.056	0.442	0.093
1 time/week	28 (17.1)	136 (82.9)	0.438		0.417	
1 time/month or less	4 (9.3)	39 (90.7)	0.215		0.231	
Butter						
Everyday	7 (35.0)	13 (65.0)	1		1	
2-3 times/week	22 (14.2)	133 (85.8)	0.891	0.406	0.818	0.379
1 time/week	33 (18.6)	144 (81.4)	1.348		1.315	
1 time/month or less	52 (17.6)	244 (82.4)	0.404		0.404	
Margarine						
Everyday	21 (21.0)	79 (79.0)	1		1	
2-3 times/week	28 (17.0)	137 (83.0)	1.127	0.411	1.074	0.320
1 time/week	20 (16.3)	103 (83.7)	0.943		0.918	
1 time/month or less	45 (17.2)	216 (82.8)	0.812		0.762	
Yogurt						
Everyday	36 (16.5)	182 (83.5)	1		1	
2-3 times/week	47 (19.3)	196 (80.7)	1.294	0.998	1.383	0.543
1 time/week	16 (14.8)	92 (85.2)	0.847		0.868	
1 time/month or less	15 (18.8)	65 (81.3)	1.048		0.942	
Natto						
Everyday	4 (6.7)	56 (93.3)	1		1	
2-3 times/week	47 (17.7)	219 (82.3)	1.129	0.021	1.242	0.020
1 time/week	38 (19.2)	160 (80.8)	1.286		1.389	
1 time/month or less	25 (20.2)	99 (79.8)	4.193		4.934	

Multiple logistic regression analysis was additionally adjusted for the mother's atopic dermatitis, season of birth and the baby's gender.

Table 3 Correlation of food consumption

Fish					
Butter	-0.001 [†]				
	0.984*				
Margarine	-0.080	0.022			
	0.043	0.569			
Yoghurt	0.073	0.081	0.094		
	0.062	0.039	0.017		
Natto	0.144	0.005	-0.063	0.178	
	<0.001	0.891	0.110	<0.001	
	Fish	Butter	Margarine	Yoghurt	Natto

[†]Correlation coefficient (Spearman's rho), **P*-value.

compared to the intake of two to three times a week or less. However, a dosage response was not found in relation to eczema in the present study. Thus, the effect of butter intake on babies' eczema should be carefully interpreted. In fact, some reports up to the

present date in Europe and Japan showed no relationship between the maternal intake of butter along with its fat ingredients during pregnancy and the babies' eczema.^{4,6,7,9} In contrast, research in Finland reported that the maternal intake of butter and saturated fatty acids during pregnancy increased the risk of the sensitization to wheat allergens of children five years old.¹⁶ More studies are needed to conclude the relation between butter intake during pregnancy and allergies in infants.

The results of the research on the relationship between the maternal intake frequency of natto during pregnancy and the babies' eczema are very interesting. In a study where *Bacillus subtilis* was dosed to human subjects, the number of clostridium in feces significantly decreased, showing that natto has the effect of improving the intestinal environment.¹⁷ In another study, water-soluble polysaccharides produced by *Bacillus subtilis* natto, called levan, were dosed to OVA-sensitized mice. Increase in in vitro IL-12 p40 and TNF- α production from macrophage, and significant decline of IgE production in OVA-sensitized mice were observed.¹⁸ Although these studies were not for the maternal intake of natto during pregnancy,

Table 4 Association between infantile eczema and maternal high consumption of five foods during pregnancy

	Infant with eczema n (%)	Infant without eczema n (%)	Crude OR		Adjusted OR	
			OR	p-value	aOR	p-value
Fish						
Every day	8 (24.2)	25 (75.8)	1		1	
2-3 times/week or less	106 (17.2)	509 (82.8)	0.518	0.132	0.755	0.514
Butter						
Every day	7 (35.0)	13 (65.0)	1		1	
2-3 times/week or less	107 (17.0)	521 (83.0)	0.376	0.044	0.373	0.053
Margarine						
Every day	21 (21.0)	79 (79.0)	1		1	
2-3 times/week or less	93 (16.9)	456 (83.1)	0.780	0.368	0.717	0.233
Yogurt						
Every day	36 (16.5)	182 (83.5)	1		1	
2-3 times/week or less	78 (18.1)	353 (81.9)	1.102	0.672	0.977	0.917
Natto						
Every day	4 (6.7)	56 (93.3)	1		1	
2-3 times/week or less	110 (18.7)	487 (81.3)	3.212	0.028	3.467	0.020

In multiple logistic regression analysis, in addition to the mother's atopic dermatitis, season of birth and the baby's gender, we included five independent terms for food intake frequency and significant (p -value < 0.05) interaction terms (fish and margarine; fish and natto; butter and yogurt; margarine and yogurt; yogurt and natto).

the improvement of the environment inside the intestines and immune regulation of the mothers' body caused by *Bacillus subtilis* natto possibly led to the decline in the incidence of the babies' eczema.

There are several limitations in this research. 1) Only intake frequencies were investigated, so that only the effects by intake habits can be known, but the effects by intake volumes cannot be known. 2) Only the intake of specific foods was recorded. It should have been necessary to survey the intake amounts of other foods and nutrients and dietary habits using a food-frequency questionnaire to investigate the "natto" effect on babies' eczema. 3) Only the frequencies of the maternal intake of food during pregnancy were recorded. Because there is a possibility that the foods that mothers take after delivery have effects on children through breast milk, it should have been necessary to grasp the maternal intake of foods not only during pregnancy but also during breast-feeding. 4) The diagnosis of eczema was not through a physician but by a questionnaire. Furthermore, as the serum IgE was not examined, it is unclear whether or not the eczema in this research was an atopic one. Furthermore, it remains to be seen whether the "natto" effect observed in the study can be seen for a longer period or for other symptoms like wheezing and food allergy.

Nevertheless, the present study suggests that the frequent intake of natto possibly inhibits development of eczema in children at 6 month of age. A large-scale intervention research is required to confirm the findings in this study.

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